

# Atrial Arrhythmia Summit: Summary Report

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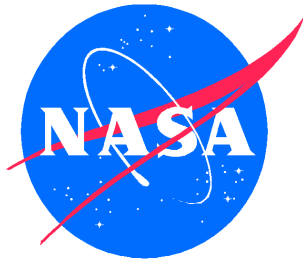
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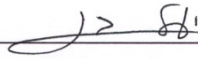
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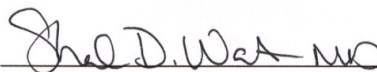
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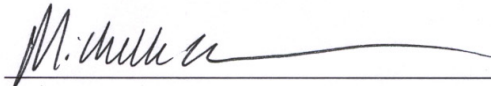
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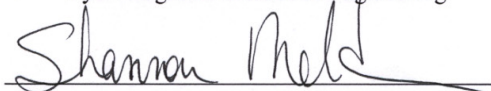
  
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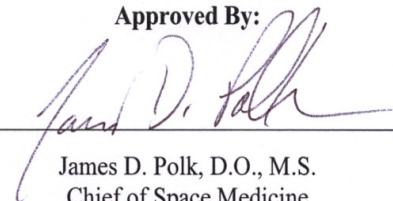
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# TABLE OF CONTENTS

	<b>Topic</b>	<b>Page #</b>
<b>I.</b>	<b>Introduction</b>	<b>1</b>
	<b>Background and Problem Definition</b>	
	<b>Summit Meeting Objectives</b>	
<b>II.</b>	<b>Summit Attendees</b>	<b>2</b>
	<b>Summit Panel Members</b>	
	<b>Summit Participants</b>	
<b>III.</b>	<b>Summit Agenda</b>	<b>5</b>
<b>IV.</b>	<b>Summary of Discussion</b>	<b>6</b>
	<b>Epidemiology</b>	
	<b>Screening</b>	
	<b>Standards and Selection</b>	
	<b>Treatment of Preflight Atrial Fibrillation</b>	
	<b>In-Flight Atrial Fibrillation</b>	
	<b>United States Air Force Experience</b>	
	<b>Prevention</b>	
	<b>Future Research</b>	
<b>V.</b>	<b>Summary of Recommendations</b>	<b>25</b>
<b>VI.</b>	<b>Summit Outcome</b>	<b>29</b>
<b>VII.</b>	<b>List of Acronyms</b>	<b>30</b>
<b>VIII.</b>	<b>Appendix 1: Panel Member Biographies</b>	<b>31</b>

# **I. INTRODUCTION**

## **Background and Problem Definition**

NASA's Space Medicine Division at the Johnson Space Center oversees astronaut health from initial selection, through training, space flight, and postflight rehabilitation. The medical standards and clinical guidelines used for screening, diagnosis, and management of medical conditions are updated periodically to reflect changes in terrestrial medical practices, or to encompass newly identified medical challenges related to space flight or its training.

To evaluate current standards and practices related to atrial arrhythmias in astronauts, Space Medicine's Advanced Projects Section was tasked with organizing a 1-day summit to discuss Space Medicine's approach to atrial arrhythmias in the astronaut cohort. Since 1959, 11 cases of atrial fibrillation, atrial flutter, or supraventricular tachycardia have been recorded among active corps crewmembers. Six additional cases have been identified among retired astronauts. Most of the cases were paroxysmal (intermittent), although a few were sustained. While most of the affected crewmembers were asymptomatic, those slated for long-duration space flight underwent radiofrequency ablation treatment to prevent further episodes of the arrhythmia. The summit was thus convened to solicit expert opinion on screening, diagnosis, and treatment options, to identify gaps in knowledge, and to propose relevant research initiatives.

## **Summit Meeting Objectives**

The Atrial Arrhythmia Summit was held on January 22, 2010 at Wyle Integrated Science & Engineering in Houston, Texas. The summit brought together a panel of six cardiologists, including nationally and internationally renowned leaders in cardiac electrophysiology, exercise physiology, and space flight cardiovascular physiology, and was chaired by Dr. J.D. Polk. Other summit participants included flight surgeons and representatives from the astronaut office, NASA's research community, the National Space Biomedical Research Institute, the NASA Longitudinal Study of Astronaut Health, and NASA's international partners. The summit panel and participants were presented with background information and atrial arrhythmia case presentations. The summit concluded with a panel discussion of directed questions posed by the summit chairman. The primary objectives of the summit discussions were:

- To evaluate cases of atrial arrhythmia in the astronaut population
- To understand the factors that may predispose an individual to this condition
- To understand NASA's current capabilities for screening, diagnosis, and treatment
- To discuss the risks associated with treatment of crewmembers assigned to long-duration missions or extravehicular activities
- To discuss recommendations for prevention or management of future cases
- To formulate clearly defined recommendations as a deliverable to the program

## **II. SUMMIT ATTENDEES**

The following is a list of the summit's panel members and participants. Panel member biographies can be found in Appendix 1 of this report.

### **Summit Panel Members**

#### **J.D. Polk, D.O., M.S., C.P.E., F.A.C.O.E.P. – Panel Chairman**

Chief of Space Medicine, NASA Johnson Space Center in Houston, Texas.

#### **J. David Burkhardt, M.D., F.A.C.C.**

Staff Electrophysiology Cardiologist, Texas Cardiac Arrhythmia Institute at St. David's Medical Center in Austin, Texas.

#### **Mohamed H. Hamdan, M.D., M.B.A., F.A.C.C., F.H.R.S.**

Professor of Internal Medicine; Associate Chief, Division of Cardiology; and Director, Clinical Cardiac Electrophysiology, The University of Utah.

#### **Rodney Horton, M.D., F.A.C.C.**

Staff Electrophysiology Cardiologist, Texas Cardiac Arrhythmia Institute at St. David's Medical Center in Austin, Texas.

#### **Benjamin D. Levine, M.D., F.A.C.C., F.A.C.S.M.**

Distinguished Professor in Exercise Science and Professor of Medicine and Cardiology, The University of Texas Southwestern Medical Center at Dallas; Director, Institute for Exercise and Environmental Medicine; S. Finley Ewing Jr. Chair for Wellness; and Harry S. Moss Heart Chair for Cardiovascular Research, Texas Health Presbyterian Hospital, Dallas; Team Leader for the Cardiovascular Alterations Team, National Space Biomedical Research Institute.

#### **Andrea Natale, M.D., F.A.C.C., F.H.R.S.**

Executive Medical Director, Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas.

#### **Richard L. Page, M.D., F.A.C.C., F.A.H.A., F.H.R.S.**

Professor and Chair, Department of Medicine, The University of Wisconsin School of Medicine & Public Health.



## Summit Participants

1. **David Alexander, M.D.** – Flight Surgeon, NASA
2. **Serena Aunon, M.D., M.P.H.** – Astronaut Candidate, NASA
3. **Ellen Baker, M.D., M.P.H.** – Astronaut, NASA
4. **Pete Bauer, M.D.** - Flight Surgeon, NASA
5. **Earl F. Beard, M.D.** – Department of Cardiology, Kelsey-Seybold Clinic
6. **Tarah Castleberry, D.O.** – Flight Surgeon, UTMB/Wyle Integrated Science & Engineering
7. **John Charles, Ph.D.** – Program Scientist, Human Research Program, NASA
8. **Matthew Dare** - Research and Technology coordinator, Texas Cardiac Arrhythmia Institute, St. David's Medical Center
9. **Eddie Davenport, M.D.** – Cardiologist, USAF Aeromedical Consultation Service
10. **Jeff Davis, M.D., M.S.** - Director, Space Life Sciences, NASA
11. **David Gillis, M.D., Ph.D.** - Advanced Projects Physician, UTMB/Wyle Integrated Science & Engineering
12. **Doug Hamilton, M.D., Ph.D.** – Advanced Projects Physician, UTMB/Wyle Integrated Science & Engineering
13. **Heather Hartnett, Ph.D.** - Lead Epidemiologist, Space Medicine, Wyle Integrated Science & Engineering
14. **Kathy Johnson-Throop, Ph.D.** – Chief, Medical Informatics & Health Care Systems, NASA
15. **Smith Johnston, M.D., M.S.** - Flight Surgeon, NASA
16. **Eric Kerstman, M.D., M.P.H.** - Advanced Projects Physician, UTMB/Wyle Integrated Science & Engineering
17. **William Kruyer, M.D.** - Chief Cardiologist, USAF Aeromedical Consultation Service
18. **Vilma Lopez, R.N.** – Advanced Projects, Wyle Integrated Science & Engineering
19. **Kathleen McMonigal, M.D.** – Manager, Clinical Laboratories, NASA
20. **Terry Pattinson, M.D.** – Medical Officer, Clinical Services Branch, NASA
21. **Steven Platts, Ph.D.** – Technical Monitor, JSC Cardiovascular Laboratory, NASA
22. **Edward Powers, M.D., M.S.** - Flight Surgeon, NASA
23. **Ashot Sargsyan, M.D.** - Advanced Projects Physician, Wyle Integrated Science & Engineering
24. **Lynn Saile, R.N.** – Advanced Projects, Wyle Integrated Science & Engineering
25. **Scott Savage, D.O.** – Flight Surgeon, UTMB/Wyle Integrated Science & Engineering
26. **Rick Scheuring, D.O., M.S.** – Flight Surgeon, NASA
27. **Kazuhito Shimada, M.D.** – Flight Surgeon, JAXA
28. **Paul Stoner, M.D.** - Flight Surgeon, NASA
29. **Terrance Taddeo, M.D.** – Chief, Medical Operations, NASA
30. **Bill Tarver, M.D.** - Chief, Flight Medicine Clinic, NASA
31. **Barbara Thomas, R.N.** – Director of Electrophysiology Services, Texas Cardiac Arrhythmia Institute, St. David's Medical Center

**Wyle Management Support:**

- 32. **Genie Bopp, B.S.** - Vice President and Crew Health & Research Department Manager, Wyle Integrated Science & Engineering
- 33. **Michelle Christgen, B.S.** – Space Medicine Group Manager, Wyle Integrated Science & Engineering
- 34. **Shannon Melton, B.S.** – Advanced Projects Section Manager, Wyle Integrated Science & Engineering

**Summit Staff:**

- 35. **Yael Barr, M.D., M.P.H.** – Advanced Projects Physician, UTMB/Wyle Integrated Science & Engineering
- 36. **Kristina Barsten, B.S.** – Advanced Projects, EASI/Wyle Integrated Science & Engineering
- 37. **Marilyn Sylvester** – Space Medicine, Wyle Integrated Science & Engineering
- 38. **Sharmi Watkins, M.D., M.P.H.** – Exploration Medical Capability Element Scientist, UTMB/Wyle Integrated Science & Engineering
- 39. **Jimmy Wu, B.S.** – Exploration Medical Capability Project Manager, Advanced Projects, Wyle

**Minute Support:**

- 40. **Deanna Barousse** – Flight Medicine Clinic, Wyle Integrated Science & Engineering

### III. SUMMIT AGENDA

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Time	Topic	Presenter(s)
8:00	Registration	
8:15	Welcome and Introductions	J.D. Polk, D.O., M.S., C.P.E., F.A.C.O.E.P.
8:20	Preflight Screening, In-Flight Capabilities, & Postflight Testing	Bill Tarver, M.D.
8:50	Epidemiological Analysis of Cases	Heather Hartnett, Ph.D.
9:00	Case Presentations	Flight Surgeons
10:00	Break	
10:15	Case Presentations	Flight Surgeons
11:30	Lunch	
12:30	Case Presentations	Flight Surgeons
1:00	Current Techniques for Treatment of Atrial Arrhythmias	Andrea Natale, M.D., F.A.C.C., F.H.R.S.
2:00	Directed Questions and Formulation of Recommendations	Panel
3:30	Break	
3:45	Directed Questions and Formulation of Recommendations	Panel
5:00	Adjourn	
5:30	Optional Tour – Mission Control Center & Astronaut Training Facility and Mockups	

## IV. SUMMARY OF DISCUSSION

Note: Since atrial fibrillation was the most common atrial arrhythmia seen in crewmembers, most of the discussion during the course of the summit centered on atrial fibrillation management. This focus is reflected in the following summary.

### **Epidemiology**

#### **Are Atrial Arrhythmias More Prevalent in the Astronaut Population or Are They Diagnosed More Frequently Because of the Extensive Screening They Undergo?**

Data presented during the summit by panel members indicated that atrial fibrillation is common in the general population, with a prevalence of approximately 6% in those over age 60 (range of 2 to 9%). Since the late 1950s, 17 cases of atrial arrhythmias have been identified among a total number of 317 active and retired astronauts, most of them diagnosed as atrial fibrillation. Since 2001, five astronauts out of a cohort of approximately 100 in the active astronaut corps underwent radiofrequency ablation treatment for atrial arrhythmias (mostly atrial fibrillation). Using the above numbers, a prevalence of 5% was calculated, which the panel felt to be consistent with the prevalence seen in the general population. However, the panel noted the much younger age at presentation among the astronaut cohort: early to mid-40s as opposed to 60 and older in the general population, with the prevalence of atrial fibrillation in the comparable 40 to 50 year-old age group in the general population being relatively low. The panel felt that the younger age distribution could be due to several factors:

- **Closer screening of the astronaut cohort** - Almost all of the atrial arrhythmia cases were asymptomatic and discovered incidentally during occupational testing. The general population is not routinely screened for arrhythmias if asymptomatic.
- **High vagal tone** - A comparable subgroup of the general population that bears some demographic resemblance to the astronauts is that of endurance-trained athletes, where a higher prevalence of atrial fibrillation at younger ages has been described in the literature. The panel members remarked that meta-analysis of atrial fibrillation among athletes shows that intense aerobic exercise beyond 200 minutes (3.3 hours) per week increases the risk of atrial fibrillation. Most astronauts exercise well beyond 3 hours per week. However, the panel noted that although the astronauts are very fit, most are not as fit as competitive athletes. The panel noted that only a few astronauts have a  $\text{VO}_2$  max over 60 ml/kg/min and the average is 46 ml/kg/min, which is lower than what would be expected from highly trained competitive athletes. Regardless, a higher vagal tone due to aerobic fitness was felt to play a possible role in the younger age at presentation among the astronaut cohort.

In conclusion, the overall prevalence of atrial arrhythmias among astronauts was not felt to be excessive compared with the general population, although the age at presentation was younger, similar to the endurance athlete population. These findings were thought to be a combination of frequent screening and perhaps a higher vagal tone due to exercise, although statistical chance as the cause could not be excluded.

### **Potential Risk Factors that may Predispose Astronauts to Atrial Arrhythmias Independent of Space Flight**

All cases of atrial arrhythmias reported among NASA astronauts have occurred terrestrially, were unrelated to space flight, and most were detected incidentally in asymptomatic crewmembers. The panel noted that a number of risk factors that can precipitate lone atrial fibrillation in the general population may be contributory in the astronaut population. Those include:

- **Gender** – Most of the cases among astronauts have been in males, mirroring the higher prevalence seen among men in the general population.
- **Hypertension** – The panel noted that there is no linear correlation between the degree of hypertension and the risk of recurrent atrial fibrillation. The panel noted that their experience has shown that approximately 25% of lone atrial fibrillation cases have undiagnosed hypertension. The panel thus recommended pursuing more aggressive blood pressure screening in all lone atrial fibrillation cases, using ambulatory blood pressure monitors instead of random blood pressure measurements obtained in the clinic. The panel noted that blood pressure does not need to be maintained in the range of 120/70 to prevent atrial fibrillation, and that such tight blood pressure control may have negative effects on G-tolerance without gaining a commensurate reduction in atrial fibrillation occurrence.
- **Endurance training** – As discussed in the above section, the panel noted that endurance training has been linked to higher rates of atrial fibrillation, through a variety of possible mechanisms, the most important being a high vagal tone, as well as perhaps increased left atrial size.
- **Alcohol** – The panel noted that the medical literature supports an association between excessive alcohol intake and the occurrence of atrial fibrillation. JSC Space Medicine management commented that both astronauts and flight surgeons are aware that alcohol intake should be minimized. The JSC Flight Medicine Clinic's evaluation of risk factors for the astronaut corp atrial arrhythmia cases found no link to alcohol intake.

The panel noted that patients presenting with paroxysmal atrial fibrillation at a young age tend to develop the arrhythmia as a triggered event rather than an underlying substrate disorder.

Additional potential triggers mentioned by the panel include **caffeine, sleep apnea, and medications** (including over-the-counter common cold medications). The panel noted that sleep deprivation was unlikely to be a risk factor.

### **Potential Space Flight-Related Risk Factors that May Predispose Astronauts to Atrial Arrhythmias**

- **Microgravity-related fluid shifts and atrial stretch** - The panel discussed the physiological changes to the cardiovascular system that occur in microgravity. Upon exposure to microgravity, headward fluid shifts cause the heart to acutely enlarge, and although the central venous pressure (CVP) has been shown to decrease, transmural cardiac pressures increase due to the larger cardiac volume. Within 48 hours of entering microgravity, circulating plasma volume is reduced (partially through diuresis and partially due to movement of fluid to the interstitial space) and the heart shrinks to a size intermediate between a standing and supine posture on Earth. Cardiac output, stroke volume, left ventricular volume, and the Renin-Angiotensin axis all adapt to this approximately halfway point between terrestrial standing and supine values. During on-orbit exercise sessions, the left ventricle transiently enlarges. While atrial enlargement and stretch could increase the likelihood of developing atrial fibrillation, the panel noted that this stretch is mild and equivalent to the atrial stretch seen in semi-recumbent terrestrial positions (between standing and supine). A summit participant reported that this has also been corroborated by the Advanced Diagnostic Ultrasound in Microgravity (ADUM) study, which measured 36 echocardiographic parameters on six ISS astronauts pre-, in-, and postflight. Measurements were obtained while supine on Earth and while floating in space and did not show any significant changes in the diastolic or systolic dimensions of any cardiac chamber between pre-, in-, and postflight states. In light of these findings, and the fact that all cases of atrial arrhythmias have occurred terrestrially, the panel concluded that microgravity-related fluid shifts are not a substantial risk factor for atrial arrhythmias in flight.
- **Space flight-induced sympathetic activation** – Activation of the sympathetic nervous system, which may contribute to atrial fibrillation, was noted by the panel members to be mild in space, and lower than the activation seen with an upright (standing) posture on Earth. A summit participant reported that a recent (unpublished) NASA project involved a review of all ECGs since STS-6, totaling 4 million heart beats on record. While sinus arrhythmia with respiratory variation was seen in 5% of preflight ECGs, it was found in 50% of ECGs recorded on orbit, most notably during EVA. The mechanism behind this phenomenon is yet to be elucidated, but a panel member noted that sinus arrhythmia is very common in the general population, and that most 12-lead ECGs or rhythm strips from young healthy individuals display respiratory sinus arrhythmia. Regardless, the panel members did not think that sympathetic activation was a risk factor for the development of atrial arrhythmias in flight.

- **Role of a high sodium diet** – Dietary sodium intake during space flight is high, with daily intakes ranging between 5 to 10 grams of sodium per day. This is due to the food preservation methods required for prolonging the shelf life of foods for long-duration missions. A high salt diet has been implicated in space flight-associated bone loss and papilledema. However, for atrial arrhythmias, there is no known direct causality of high sodium intake independent of hypertension. The panel noted that certain individuals may be salt sensitive, such that a sodium-rich diet could lead to an increase in circulating blood volume and therefore an increase in atrial stretch that could contribute to atrial arrhythmias. The panel suggested preflight testing of crewmembers with a 2-week diet of space flight foods, and a subsequent measurement of atrial volume and filling pressures. The panel recommended lowering the daily dietary salt intake to 5 grams or less per day. The panel also noted that studying sodium balance during space flight has been challenging because the data acquired were influenced by a variety of circumstances and practices. According to the Henry Gauer hypothesis, a salt and water diuresis is expected in the first two days of space flight, however this is usually masked by crew members' lower intravascular volume caused by voluntary preflight dehydration, feet-up launch position, and emesis related to space motion sickness. These factors lead to a lowered effective circulating blood volume and decrease the expected natriuresis. The panel members noted that a steering committee summarizing the last decade of NASA research agreed that placing an individual with a stable salt and water content in microgravity with a constant intake of salt and water and no emesis or dehydration, would unmask a salt and water diuresis consistent with the Henry Gauer reflex.
- **Chronic radiation exposure** – A summit participant commented that chronic radiation exposure was evaluated at a recent Lunar Exploration ECG meeting as a possible, though hypothetical, contributor to arrhythmias. JSC Space Medicine management noted that radiation exposure is tracked by the NASA radiation officers with both personal dosimeters and environmental monitors, and that both quantitative and qualitative dose calculations are available for each astronaut.

The panel concluded that there is no evidence at this time that any variable of the space flight environment increases the likelihood of developing atrial arrhythmias during space flight.

## **Screening**

### **Recommended Changes to Current Screening Practices**

- **Treadmill testing for arrhythmia and ischemia screening** – The current cardiac screening of astronauts post-selection uses a modified Bruce protocol treadmill stress test performed to 85% of the maximum predicted heart rate for at least 9 minutes. This is in contrast to the screening conducted during astronaut selection, which involves a maximal performance treadmill test, and is also in contrast to a maximal performance  $\text{VO}_2$  bicycle test done for determination of functional capability as a pre-launch requirement for ISS missions. The panel members recommended using the maximal exertion protocol for evaluating both ischemia and arrhythmia risk in crewmembers, noting that stopping at 85% of max predicted heart rate is not sufficiently sensitive for diagnosis of these medical issues. The panel recommended that a symptom-limited endpoint be pursued, as this will provide a functional evaluation that has important prognostic information. The panel conveyed their understanding of the wish of astronauts to pass each medical test, but felt that it is the flight surgeons' obligation to provide the astronauts with an opportunity to undergo full testing so that appropriate risk stratification can be performed. The panel noted that a positive test does not necessarily mean the astronaut is disqualified from space flight, but can be used for flight planning purposes; for example, observation of exercise-induced atrial fibrillation may call for a beta blocker tolerance test and augmentation of the space flight medical kit with beta blockers for the crewmember to use should the need arise. The panel agreed that the on orbit Periodic Fitness Exam should continue. The Periodic Fitness Exam is done monthly during long-duration ISS missions, utilizing the modified protocol (85% of the crewmember's predicted terrestrial  $\text{VO}_2$  max) and monitored with a derived 12-lead ECG.
- **Interpreting low positive predictive values of screening tests in a population with low pretest probability** - The panel discussed the challenge of using screening tests that have a low positive predictive value in a population with a low pretest probability, and how to best proceed when such a test is positive. Cardiovascular screening tests are usually best when used on a population with a medium to high pretest probability; however the astronaut population has a low pretest probability for cardiac conditions, making a positive test result more likely to be a false positive, which might lead to unnecessary disqualification of healthy individuals. A panel participant noted that, in space medicine, it may be more meaningful to use the negative predictive value of tests. The panel's recommendation was that given the possible career and mission impacts of medical conditions in the astronaut population, positive test results should be followed with a definitive test (such as a coronary catheterization or an electrophysiology study) even if suspected to be falsely positive. As such, given the human and financial cost of cardiac complications during space flight, aggressive screening is warranted.



## **Potential Novel Screening Tests**

JSC's Space Medicine division is interested in novel noninvasive tests that could be used to screen asymptomatic astronauts to identify those susceptible to developing atrial arrhythmias. The panel listed the following novel screening tests for potential future use, noting that these techniques have not yet been proven with prospective and longitudinal studies, and their sensitivity, specificity, and positive/negative predictive values are yet to be determined:

- 1) **Long-term Holter monitoring (7 to 20 days)** – The panel recommended replacing the current 24-hour Holter monitoring, done at selection to the astronaut corps as well as during preflight screening before long-duration ISS missions, with longer term Holter monitoring, recording for 7 to 20 days. The panel commented that this has become a standard in some health care institutions.
- 2) **High resolution Holter looking for rate dependence and changes in conduction delay in the atria** – The panel commented that certain findings on Holter monitoring done during sinus rhythm may indicate dual path physiology that is the substrate for atrio-ventricular nodal reentrant tachycardia (AVNRT). These subtle findings include abrupt changes in PR interval, echo beats, and other changes and could be identified with careful analysis of the Holter tracings. Patients manifesting these changes may then be treated preventively before they become symptomatic. The panel recommended that Holter tracings be read by cardiologists familiar with the space flight milieu, since what would otherwise be considered unremarkable in the general population may be consequential in the astronaut population. The panel suggested that the criteria for reading the Holter tracings may need to be different and more rigid for astronauts compared to the general population.
- 3) **Cardiac MRI looking at scar burden** - Although patients with atrial fibrillation may have otherwise normal hearts, cardiac MRI may still reveal scarring, which some believe can be used in predicting the recurrence rate post-ablation or other treatments. This test has not yet been used to look at de-novo occurrences of atrial fibrillation in those without a prior history of the arrhythmia. Not all panel members were in agreement regarding the value of scar burden as a predictor of future atrial fibrillation.
- 4) **Gene analysis** – The panel recommended banking of astronaut blood samples for genetic testing. Several panel members cautioned that, at present, limited technology and knowledge preclude any meaningful result from testing in such a small cohort. Those panel members cautioned that the current number of cases among the astronaut corps is too small to gain insight into genome associations. Aside from sodium-potassium channels or connexin channels, the knowledge of which genetic variables may be contributory is not currently available. Those panel members noted that such genome associations will have to be derived

from large population-based studies that can follow thousands of individuals over time before they can be applied to astronaut genetic testing. Other panel members maintain that the field of genetic testing is rapidly evolving and that sufficient background data has been accumulated to date to support gene evaluations in astronauts despite the small astronaut cohort.

Several panel members recommended avoiding screening tests that have not yet proven their effectiveness or safety on a large population basis. For example, they cautioned that MRIs with gadolinium performed only for the purpose of identifying atrial fibrillation susceptibility may cause more harm, through complications such as nephrogenic sclerosis, than identify atrial fibrillation susceptibility. The panel members noted that monitoring is currently the safest option for early diagnosis. In addition, the panel members commented that with continued data acquisition, the collected information (including the false positives) would allow for more accurate future data analysis and interpretation in addition to illuminating potential risks and side effects of the test or materials used to perform the test.

## **Standards and Selection**

### **Standards for Atrial Fibrillation in Pre-Selection Astronaut Candidates**

The current NASA standards for selection into the astronaut corps disqualify applicants with a current diagnosis of atrial fibrillation or atrial flutter. A history of a single episode of atrial fibrillation or atrial flutter without hemodynamic symptoms, or a history of ablation treatment, will require workup including, in some cases, cardiac catheterization. The panel felt that because there are sufficient numbers of highly qualified individuals that compete for selection into the corps, stricter selection criteria can be implemented, and those with a history of prior atrial fibrillation (including those who have undergone ablation and are considered “cured”) should be disqualified. The panel remarked that the risk of atrial fibrillation recurrence will always be higher in those with prior atrial fibrillation (whether ablated or not) compared with an individual who is atrial fibrillation naïve. Even with ablation, there is approximately an 8% recurrence rate of atrial fibrillation, which is substantially higher than the background risk for a young healthy person.

The panel also remarked that no test, such as an electrophysiology (EP) study or a gated MRI to look for scar burden, can guarantee that an ablated individual will never develop atrial fibrillation again; there is always some risk. For initial selection, the panel noted that there are currently no established predictors for future development of atrial fibrillation other than a history of atrial fibrillation or ablation, assuming the applicants are relatively normotensive, fit, and have structurally normal hearts. Several of the panel members reflected that a family history of arrhythmia is not adequately predictive of arrhythmia development in the candidate and should not constitute a basis for disqualifying an astronaut applicant during initial selection. Other panel members noted that, in their experience, history of atrial fibrillation in both parents does become a predictor for future development of this arrhythmia in their offspring, and therefore strong family history should be considered a possible disqualifier during astronaut selection.

### **Standards for Atrial Fibrillation in a Trained Astronaut**

The panel proposed that once an astronaut is a trained asset, is part of a relatively small pool of space flight qualified and trained individuals, and after sizable resources (time and money) have been invested in crew training, it is reasonable to allow him or her to fly, if the astronaut has undergone ablation and is asymptomatic. The current NASA waiver guide states that astronaut mission training may resume 6 months post-ablation, and that space flight can be approved 12 months post-ablation, which the panel thought reasonable. The panel agreed that development of atrial fibrillation during a 6-month mission would not likely be catastrophic in consequence and would likely be well tolerated by the affected crewmember.

## **Treatment of Atrial Fibrillation Manifesting Preflight**

### **Recommended Pharmacological Terrestrial Treatment**

The panel noted that most of the astronaut cases of atrial fibrillation presented with a relatively slow ventricular response rate. The panel remarked that possible reasons for a spontaneously well controlled ventricular response rate while in atrial fibrillation include intrinsic conduction disease, taking a nodal blocking agent, having vagally induced atrial fibrillation (generally manifesting postprandially or nocturnally), or being very fit, with the last-mentioned reason being the most likely mechanism among astronauts. The slow ventricular response rate can also explain the relative lack of symptoms, since with lower rates the patient is more likely to be asymptomatic. The panel noted that athletes tend to have higher vagal tone and tend to be more rate-controlled spontaneously, and that the best marker is the resting heart rate when in sinus rhythm. An individual whose resting heart rate is in the 40s is likely to maintain rate control when in atrial fibrillation if at rest. However, if a crewmember were to exercise while in atrial fibrillation without the influence of an atrio-ventricular nodal blocking agent, vagal tone will be withdrawn as the sympathetic nervous system is engaged, and the ventricular response rate would be expected to rapidly increase (up to rates of 200s within 3 minutes of the Bruce protocol). The increased heart rate would likely lead to the patient becoming symptomatic. Therefore, despite having good rate control at rest, astronauts would need an atrio-ventricular nodal blocking agent to provide rate control during activity.

A discussion was also held regarding preferred anti-hypertensives in those without atrial fibrillation, which could help minimize the development of the arrhythmia. Beta blockers are not used at NASA as anti-hypertensives due to their low efficacy for this indication, concerns for orthostatic intolerance, and the baseline bradycardia that is common among crewmembers. Angiotensin Converting Enzyme Inhibitors (ACEI) are preferred for treatment of hypertension. The panel concurred with avoidance of beta blockers for hypertension and noted that ACEI are preferable for treatment of hypertension as they help prevent some of the cardiac fibrosis, scarring, remodeling and inflammation caused by aldosterone (statins were noted to have a similar effect). Other classes of anti-hypertensive medications (including beta blockers) do not have this beneficial effect.

### **Potential Complications from Ablation that May Impact Crewmembers Assigned to Long-Duration Missions or Extravehicular Activities**

An iatrogenic atrial septal defect is a possible complication from the ablation procedure that would be a concern for astronauts assigned to extravehicular activities (EVA), since the lower pressure in the EVA suit can give rise to intravascular nitrogen bubbles that may pass through the septal defect, enter the arterial circulation, and behave like an embolus. The panel explained that, in 75% of ablation cases, intracardiac echo used during the ablation procedure demonstrates that elastic tissue recoil closes any iatrogenic septal defects at the conclusion of the procedure. Any remaining openings are likely to close within a few weeks post-procedure. The panel noted that all cases they have treated with a re-ablation procedure 2 months after the initial procedure have shown complete closure with no remnants from the previous procedure. However, this risk depends on the technology and equipment used during the procedure. Some of the newer and larger 16 F balloons used today in balloon-based procedures have been implicated in post-ablation septal defects, but use of the conventional catheter size is considered to be safe and should not lead to this complication.

### **Post-Ablation Recurrence**

The panel noted that failure rates during the first year post-ablation are dependent on multiple variables and thus difficult to predict and measure. Long-term success after one or two ablation procedures depends on the type of procedure performed, the experience of the operator, and patient characteristics (including type of arrhythmia); some patients require more than one procedure and are more difficult to treat. Outcome for accessory pathways or WPW ablation is excellent and can be considered curative, as the incidence of recurrence is very small. The rate of atrial fibrillation after atrial flutter ablation is higher, with 85% of those undergoing ablation for atrial flutter developing atrial fibrillation after 5 years and, in cases where cryo-ablation was used, recurrences are seen as soon as 1 year post-ablation. Despite the relatively high rate of atrial fibrillation after ablation for atrial flutter, it is not customary to prophylactically ablate for atrial fibrillation while ablating the atrial flutter, but monitoring is employed to detect occurrence of atrial fibrillation. However, certain patients will manifest both atrial flutter and atrial fibrillation during the EP study, and will thus undergo ablation for both arrhythmias. Of the atrial arrhythmias, atrial fibrillation has a more unpredictable and higher recurrence rate, but there is variation in the individual institutions' reported successes, with some reporting up to 30% late recurrences and others reporting less than 10% late recurrences. In one panelist's experience, the 1-year late recurrence rate is approximately 8%, and is more frequent in cases of chronic atrial fibrillation, and less common in the paroxysmal cases; other panelists were concerned that recurrence was more common. Among the paroxysmal cases, more recurrences are seen among women, in patients with sleep apnea, and to a lesser degree, in athletes.

The panel debated whether atrial fibrillation can be considered cured following ablation. Some of the panel members maintained that atrial fibrillation is never cured and, regardless of operator experience and extent of the ablation, the likelihood of atrial fibrillation remains higher in those who have had atrial fibrillation or atrial fibrillation ablation; they felt that the frequency of recurrence depends on how aggressively one investigates. A minority of panel members disagreed, maintaining that a cure is possible with proper ablation and that the studies where recurrences were seen were not controlled for the type or extent of the ablation procedure, nor for operator experience or patient characteristics.

The panel also highlighted the importance of the monitoring protocol used post-ablation in defining recurrences. Panel members noted that in their own practices post-ablation patients are given an event recorder and requested to transmit recordings several times per week, even if asymptomatic. In addition, a 7-day Holter is recorded every 3 months. This close monitoring regimen identifies patients who have very short episodes of recurrent atrial arrhythmia, which are considered recurrences from the physician's standpoint, but warrant treatment only if they become longer and more clinically relevant. Most recurrences were believed to manifest within the first 6 months post-ablation. The panel noted that the risk for post-ablation recurrence will not be reduced by preventive care. Recurrences might be minimized by a more aggressive initial ablation procedure.

The panel commented that the astronauts are a unique patient population, as they do not have structural heart disease, and their atrial fibrillation is paroxysmal in nature. Atrial fibrillation causes cardiac remodeling where each episode of atrial fibrillation may further increase the likelihood of recurrence. The close screening of crewmembers and their diagnosis and treatment at an early stage in the remodeling process suggest that the progression of this process may be halted (assuming that the remodeling is only due to prior episodes of atrial fibrillation and there is no remodeling associated with concurrent inflammation or other causes). For this reason, the success rate of ablation and the likelihood of achieving a post-ablation cure in this population are high. The panel suggested that recurrence in this patient population is generally dependent on whether they have electrical reconnection of the isolated ablated pulmonary veins as opposed to progression of cardiac disease. The current clinical standard of post-ablation care involves monitoring of patients and intervening only in cases that manifest a clinically significant recurrence. However, it is possible to perform an invasive diagnostic study several months after the ablation to confirm that the pulmonary veins are indeed isolated and electrically silent, especially if a crewmember is being considered for a Mars mission. The panel noted that, in several small studies, ablated patients with and without clinical recurrence consented to a diagnostic post-ablation procedure intended to check the electrical isolation of their pulmonary veins, and reconnection of the pulmonary vein electrical circuits was found to partially correlate with clinical recurrence. Among those patients with reconnection, the degree of conduction

correlated with recurrences as well, with a significant delay in the veins' conduction being associated with less recurrences compared with those whose veins conducted more rapidly.

The panel debated the question of whether re-ablation should be undertaken in an astronaut whose hypothetical post-ablation diagnostic study confirmed electrical reconnection, if asymptomatic and showing no evidence of clinical recurrence. Although in the general population re-ablation would not be considered without a clinically significant recurrence, several of the panel members felt that in the astronaut group of patients, it would be reasonable to re-ablate if there was evidence of a reconnection rather than to disqualify them from further space flight. However, other panel members cautioned that there is still insufficient evidence to support this practice, as case-controlled longitudinal studies have not been conducted to evaluate the risk versus the benefit of this proposed retreatment, and the few studies that were mentioned had small numbers of subjects. A study led by Dr. Natale showed that of those who had clinical recurrence (including cases of chronic, persistent, and paroxysmal atrial fibrillation) 85% had electrical reconnection. However, a control group of patients without clinical recurrence was not available for comparison of the rate of electrical reconnection.

The panel concluded that in the astronaut patient group, with no structural heart disease, a recent diagnosis of atrial fibrillation, and very good overall health, if veins were proven to be completely isolated, their odds of having a recurrence of atrial fibrillation would be less than 4% per year.

### **Complications Related to Ablation**

The panel commented that the perception that more extensive ablation results in a higher complication rate is not correct. Specifically, the risk of pulmonary vein stenosis does not correlate with how much tissue is ablated but rather the anatomic location of the ablation, with a higher rate of stenosis occurring if the ablation is done from within the pulmonary vein itself. Use of intracardiac echo imaging to ascertain that the ablation is performed outside of the pulmonary vein is important in minimizing this risk. However, in general, the panel agreed that the longer the duration of the procedure the higher the risk of complications.

### **Atrial Fibrillation and Anticoagulation**

Patients with atrial fibrillation are treated with anticoagulation based on their CHADS<sub>2</sub> score (Table 1), a risk assessment score created specifically for atrial fibrillation patients and used to assign anticoagulation treatment to those at risk for a CVA caused by a thromboembolus forming in the fibrillating atria.

Table 1: The CHADS<sub>2</sub> Score

Risk Factor	Points
<b>C</b> Congestive heart failure (recent)	1
<b>H</b> Hypertension	1
<b>A</b> Age ≥ 75 years old	1
<b>D</b> Diabetes	1
<b>S<sub>2</sub></b> Prior stroke / TIA	2

The panel members noted that anticoagulation following atrial fibrillation ablation is somewhat controversial. Per the guidelines, stroke risk assessment includes the yearly risk driven by the CHADS<sub>2</sub> score, and the risk of stroke associated with ablation or cardioversion. Most astronauts with atrial fibrillation, whether the atrial fibrillation occurs preflight or in flight, have a CHADS<sub>2</sub> score of 0 or 1, meaning their likelihood of atrial fibrillation-related thromboembolic CVA is very low. Since the risk of bleeding on anticoagulation is greater than the risk of a stroke for patients with a CHADS<sub>2</sub> score of 0 or 1, these patients can be treated with aspirin (ASA) alone as a preventive measure. There was less agreement among the panel members on the approach to an astronaut with a history of ablated atrial fibrillation, a history of hypertension and CVA, and a CHADS<sub>2</sub> score of 3. Some panel members advocated following the guidelines that suggest continuing anticoagulation treatment indefinitely, since a history of stroke is the greatest predictor for recurrent stroke. Other panel members noted that it is their practice to stop anticoagulation one year post-ablation if atrial fibrillation has not recurred. These panel members maintained that new data suggest this practice is safe; a study of 3,000 patients showed that among 400 of them who had a CHADS<sub>2</sub> score of > 2 post-atrial fibrillation ablation, risk of stroke was lower than in the control population of the Framingham study after anticoagulation was discontinued. Some of the panel members argued that if one is certain the CVA was caused by the atrial fibrillation and the atrial fibrillation has resolved with ablation, the risk of CVA is greatly reduced, and it is reasonable to return a crewmember to flight status on ASA only. Other panel members noted that the hypothesis that elimination of the arrhythmia will eliminate the risk of recurrent stroke has not been proven, and cautioned that despite data to suggest that the risk is very low, the knowledge base is insufficient and would warrant erring on the side of caution.

It was the panel's consensus that a crewmember who has had an atrial fibrillation-related stroke should not participate in either short- or long-duration space missions. Noting that while the likelihood of events might be low, the consequences of a CVA in flight could be catastrophic, and there is lack of data to support that flying such an individual would not jeopardize the crewmember and the mission. The panel suggested that this might be a patient who could benefit from a repeated EP study to check for venous reconnection, as it would strengthen the conviction that the likelihood of atrial fibrillation (and subsequently stroke) is low.



## **Atrial Fibrillation in Flight**

### **The Atrial Kick in Microgravity - Implications of its Loss with Atrial Fibrillation during Space Flight**

The panel noted that the atrial kick functions normally in microgravity, but that the atrial kick dynamics are slightly different in flight compared with a terrestrial supine state; in flight the early filling fraction is decreased while the atrial filling fraction is increased. Nonetheless, the atrial kick is effective in maintaining blood flow across the mitral valve and overall cardiac output. This was confirmed by the Braslet study looking at the in-flight right ventricular echocardiograms of six ISS crewmembers. While the atrial kick is larger and more significant in microgravity, the panel concluded that loss of the atrial kick during atrial fibrillation would not have a great impact on cardiac output during space flight.

### **Rate Control for Atrial Fibrillation Developing in Flight**

The panel noted that the terrestrial standard of care for stable new onset atrial fibrillation includes initial treatment with rate control and anticoagulation. The panel recommended supplying a rate control medication for Exploration-class missions in a quantity sufficient to treat at least one crewmember for the duration of the mission, should atrial fibrillation manifest in flight. However, the panel noted that titration of the rate control may be challenging; even in otherwise healthy individuals on Earth, adequate rate control is not clearly defined and an empiric figure of 80 to 90 beats per minutes (BPM) is generally used. The panel noted that a large part of the increase in heart rate is compensatory, balancing the decreased cardiac output, which stems from loss of the atrial kick and the irregular rhythm. The panel also noted that, in microgravity, where fluid shifts and the consequent physiological changes result in more preload dependence, a slightly higher rate (above 100) may be needed for compensation. Thus the panel thought that the threshold for implementing rate control **in cases of paroxysmal atrial fibrillation** should be higher in microgravity and that a less aggressive rate control regimen should be used, keeping in mind that these patients have normal hearts, are preload dependent, and are using compensatory tachycardia to maintain their cardiac output.

However, the panel cautioned that prolonged tachycardia **with chronic persistent atrial fibrillation** may lead to development of tachycardia-induced cardiomyopathy. Therefore, the panel recommended that cases of chronic persistent atrial fibrillation be maintained with a ventricular response rate below 100.

The panel members recommended that rate control be achieved using a mild AVN blockade intended to blunt a maximal ventricular response to exercise to just below 200 BPM. The panel felt that exercise tolerance would not be adversely affected by such a regimen.

The panel was divided in their preference of using a beta blocker versus a calcium channel blocker (both oral) for in-flight rate control. The panel noted that both medications will likely worsen post-landing orthostatic intolerance and will lower g tolerance. Historically, NASA preferred beta blockers because of the USAF success with their use, and most of the NASA and USAF experience with terrestrial rate control to date has been with beta blocker use. A few of the panel members favored beta blocker use for space flight, noting that low doses are generally well tolerated. The panel members also added that, during space flight, astronauts are likely to be sensitive to the action of vasodilating medications due to being mildly vasoconstricted as a compensatory mechanism to the lower circulating plasma volume. This vasodilation sensitivity would manifest during hemodynamic challenges such as physical activity (including EVA), thermal stress, and upon return to a gravitational load. Other panel members favored calcium channel blockers, especially for cases of paroxysmal atrial fibrillation, quoting a greater effectiveness at slowing the rate during episodes of arrhythmia while having a milder effect on the heart rate when in sinus rhythm, as most of the astronauts are bradycardic at baseline. Panel members in favor of calcium channel blockers also noted that side effects, such as depression, are more common with beta blockers, especially among younger patients. The panel suggested conducting preflight ground testing for crewmembers with both of these medications for a 2-week period.

The panel concluded that atrial fibrillation would most likely be well tolerated in microgravity and that, without a prior history of atrial fibrillation and with a normal heart, most cases of de novo atrial arrhythmia would probably convert back to sinus rhythm spontaneously. Symptoms should be dealt with as they develop, with rate control implemented based on the ventricular response rate.

### **Deorbit Considerations**

The panel remarked that a crewmember with atrial fibrillation who became clinically unstable (hypotensive, in heart failure, or with an uncontrolled heart rate) would likely be returned to Earth for treatment, but that stable cases can be treated on board. JSC Space Medicine management noted that the decision to deorbit a sick astronaut is a challenging one, as the golden hour of opportunity should not be missed, lest a crewmember decompensate to the point where transport back to Earth would become too risky and may not be survivable.

### **Atrial Fibrillation Induced Pulmonary Edema**

A summit participant noted that in microgravity there is no dependent protection of the lung zones from fluid overload related to heart failure. While loss of rate control on Earth could lead a patient to develop mild dyspnea and basilar crackles, in microgravity all lung zones could be in jeopardy, with the same degree of heart failure leading to diffuse lung involvement manifesting as fulminate pulmonary edema.

Panel members noted that treatment of in-flight pulmonary edema may be aided by using the Russian Braslets (cuffs that inflate around the upper thighs and once tightened increase the venous outflow pressure leading to venous pooling of blood in the lower extremities). Braslets sequester blood in the lower extremities, instantaneously mimicking the hemodynamics of giving a patient nitroglycerin or having them sit up, both being common treatments for patients with pulmonary edema. The Braslets along with more conventional treatments such as diuretics can be used while waiting for the oral rate control medication to take effect, or while awaiting orbital mechanics to allow a deorbit opportunity, which may be delayed by up to 19 hours.

### **Atrial Fibrillation, Stroke, and Anticoagulation in Flight**

The panel noted that one of the biggest concerns with development of atrial fibrillation during space flight is thrombus formation in the atria with potential embolic stroke. The panel stressed the potential catastrophic consequences of a CVA occurring on orbit. The likelihood of forming an atrial thrombus increases after 48 hours of atrial fibrillation, but thrombi can form as soon as 6 hours into the arrhythmia. Terrestrially, patients with paroxysmal atrial fibrillation who refuse anticoagulation are cautioned to seek treatment if the arrhythmia lasts more than 24 hours. The panel members noted that our understanding of embolic risk during space flight is presently lacking. Anticoagulation is not currently approved for in-flight treatment, but ASA may be used. Per the current terrestrial clinical practice guidelines, 81 to 325 mg of ASA daily is recommended for patients with atrial fibrillation who cannot or will not take anticoagulation. However, most of the panel members noted that, in their practices, they still follow the previously recommended 325 mg due to studies supporting its use, and recommended using this higher dosage for cases of atrial fibrillation manifesting in flight. The panel also noted the dichotomy of practice in cardiology where a patient with atrial fibrillation for longer than 48 hours will need anticoagulation prior to cardiac rhythm conversion even with a CHADS<sub>2</sub> score of zero, yet a patient with paroxysmal atrial fibrillation who may be in atrial fibrillation for intermittent periods of 48 hours or longer and a CHADS<sub>2</sub> score of 0 or 1 can be maintained on ASA alone.

## **United States Air Force Experience**

Over the past 50 years, the USAF School of Aerospace Medicine has seen approximately 300 to 350 fliers with atrial fibrillation, half of which were asymptomatic and discovered incidentally on exam, and half of which presented clinically with palpitations and very rarely with hemodynamic symptoms. Most of them had a ventricular rate of  $< 100$  at rest due to their good physical fitness. The USAF does not use anti-arrhythmic medications. Beta blockers (atenolol and metoprolol) are the only pharmacological agents allowed.

Pilots with paroxysmal or chronic persistent atrial fibrillation can be returned to flying status in a low-g aircraft on beta blockers without functional consequences. However, the situation is more complex for fighter pilots flying high performance jets where g-tolerance is reduced by the atrial fibrillation itself, as well as by the beta blockers used for rate control. Hence, ablation is the only treatment that can return a pilot to a high performance single-seat aircraft. The USAF has done ablations on 12 such pilots with all of them successfully returning to flight. Some of the low-g pilots may elect to undergo ablation as well, due to the better quality of life that such treatment affords. Pilots are placed on Duty Not Including Flying (DNIF) status for 6 months post-atrial fibrillation ablation, and for 4 months post-AVNRT ablation.

One difference noted between the operational environment in which USAF fighter pilots operate, in comparison to that in which NASA astronauts operate, is g exposure. USAF fighter pilots are exposed to z-axis (head-to-foot) g forces of up to 9g, and atrial fibrillation decreases their capability to maintain brain and eye perfusion in defiance of such loads. In contrast, space flight g exposures occur during launch and landing phases of flight, and are mostly in the x-axis (chest-to-back) during launch on either the space shuttle or the Soyuz, and during landing in the Soyuz (shuttle landings involve a z-axis g exposure of approximately 1.2g). Presence of atrial fibrillation is not expected to be an issue with such exposures. The NASA administrative g exposure limit is 4.5g. However, ballistic Soyuz reentries can subject a crewmember to up to 10g. A short run of ventricular tachycardia was noted in one crewmember when subjected to these higher ballistic g loads. While the Soyuz is not piloted like an aircraft or the shuttle, landing procedures are not necessarily automated and crewmember landing procedures may include switch or button actuation and requires an alert and functional crewmember. Another operational difference noted was that USAF pilots can be monitored daily and their missions are several hours long, while NASA astronauts cannot be monitored as closely during space flight, and missions may last weeks to months to years.

The USAF also maintains that AVNRT ablation is considered curative, while atrial fibrillation ablation is not.

## **Prevention of Atrial Fibrillation**

The panel noted that unlike the case of coronary artery disease where risk factors are well understood, little is known about risk factors for atrial fibrillation. In addition, atrial fibrillation is a diverse entity, with some cases being vagal in origin and some being sympathetically mediated. The following were general recommendations discussed by the panel for potential prevention:

- **Minimize risk factors for coronary artery disease** - Due to overlap of risk factors for coronary artery disease with risk factors for atrial fibrillation, minimizing risk factors for one should have a beneficial effect on minimizing risk factors for the other.
- **Statins and ACEI** – Statins and ACEI may be beneficial for atrial fibrillation risk modification due to their favorable effect on cardiac remodeling.
- **Fish oil supplements (Omega-3 fatty acids)** - Several of the panel members noted that research data point to the possible effectiveness of omega-3 fatty acids in reducing the occurrence of atrial fibrillation. Other panel members cautioned that there are some data to suggest that Omega-3 fatty acids may be proarrhythmic, although those data were obtained from patients with cardiac devices and might not extrapolate to the astronaut population. JSC Space Medicine management noted that omega-3 fatty acids are a part of the astronauts' diet and that fish oil nutritional supplements have been recommended, partly because of anecdotal evidence of its positive effect on bone health. However, there is currently no NASA protocol for omega-3 supplementation.
- **Moderate aerobic fitness** – While good aerobic fitness will not prevent the occurrence of atrial fibrillation, the elevated vagal tone that accompanies such fitness may help control the rate once atrial fibrillation has developed, mitigating symptom presentation. However, the panel cautioned against using atrial fibrillation as a rationale for determining astronaut fitness needs for missions, and noted that fitness criteria should be based on the demands of the mission. Recent publications indicate that training to the equivalent level of a competitive endurance athlete can increase the likelihood of developing atrial fibrillation. In addition, changes in vagal tone, particularly during long-duration flights may further exacerbate this risk.
- **Minimize alcohol consumption** - The medical literature supports an association between excessive alcohol intake and the occurrence of atrial fibrillation, hence minimizing alcohol consumption is advised as a preventive measure.

## **Future Research**

The panel suggested the following research areas as having potential for understanding atrial fibrillation risk factors and reducing the incidence of atrial fibrillation in astronauts:

- **Holter data analysis** – The panel suggested that modern signal processing techniques can be used to analyze high-resolution Holter studies that are already being collected on a regular basis on all crewmembers, and a database can be developed for analysis and identification of markers that can predict future atrial fibrillation. Analysis can include changes in PR interval, changes in P-wave morphology, and P-wave signal averaging. The panel felt that adding a Portapress monitor (a beat-to-beat noninvasive blood pressure monitor) would not add useful information to this analysis. A current study is examining 12 ISS crewmembers with high resolution Holters, echocardiograms, and gadolinium enhanced MRI pre- and postflight to evaluate conduction properties, atrial function, structural changes, and evidence of inflammation or fibrosis. The study will elucidate whether space flight results in atrial scarring, and is expected to enhance understanding of the cardiac substrate and help predict which parameters increase the likelihood of developing atrial fibrillation.
- **Large population-based studies** – The panel noted that NASA is not equipped to carry out the large scale population-based studies necessary to answer the key questions of who is likely to develop atrial fibrillation. Research done exclusively on the small astronaut population is not sufficient to derive this information. The panel recommended partnering with epidemiologists, geneticists, and medical institutions for this purpose, and then extrapolating data from the general population to the astronaut population. Additionally, the panel suggested looking at current clinical databases that have relevant data that could be queried to address some of these questions.
- **Genetic studies** – As outlined in the screening section above.

## **V. SUMMARY OF RECOMMENDATIONS**

### **Epidemiology**

- The panel recommended pursuing more aggressive blood pressure screening in all cases of lone atrial fibrillation, using ambulatory blood pressure monitors instead of random blood pressure measurements obtained in the clinic (Page 7).
- The panel suggested preflight testing of crewmembers to evaluate for salt sensitivity that could lead to an in-flight increase in atrial stretch that may contribute to atrial arrhythmias. Preflight testing was suggested to include a 2-week diet of space flight foods (known to be sodium rich), and a subsequent measurement of atrial volume and filling pressures. The panel recommended lowering the daily dietary salt intake to 5 grams or less per day (Page 9).

### **Screening**

- The panel recommended using the maximal exertion protocol for evaluating both ischemia and arrhythmia risk in crewmembers (Page 10).
- Given the possible career and mission impacts of medical conditions in the astronaut population, the panel recommended that positive results on screening tests should be followed with a definitive test even if the screening test is suspected to be falsely positive (Page 10).
- The panel recommended that Holter tracings be read by cardiologists familiar with the space flight milieu, since what is otherwise read as unremarkable in the general population may be consequential in the astronaut population. The panel suggested that the criteria for reading the Holter tracings may need to be different and more rigid for the astronauts compared to the general population (Page 11).
- The panel listed the following novel screening tests for potential future use, noting that these techniques have not yet been proven with prospective and longitudinal studies, and their sensitivity, specificity, and positive/negative predictive values are yet to be determined: (1) High resolution Holter monitoring looking for rate dependence and changes in conduction delay in the atria, (2) Cardiac MRI looking at scar burden, (3) Gene analysis, and (4) Long-term Holter monitoring (7 to 20 days) (Page 11).
- The panel recommended avoiding tests that have not yet proven their merit on a large population basis (Page 12).

## **Standards and Selection**

- The panel recommended that a history of atrial fibrillation should be a disqualifier during astronaut selection, noting that a candidate who has never had atrial fibrillation will have a lower likelihood of developing atrial fibrillation, and subsequently might be a safer choice compared with a candidate who has had atrial fibrillation. However, when a fully trained astronaut in whom the space program has made significant investment is diagnosed with atrial fibrillation, a decision needs to be made based on absolute risk vs. the benefit of flying that particular crewmember (Page 13).

## **Treatment of Atrial Fibrillation Manifesting Preflight**

- Although most astronauts have a baseline bradycardia at rest secondary to good aerobic fitness, the panel recommended a nodal blocking agent for periods of activity, as heart rate is expected to markedly increase during activity, and the patient is likely to become symptomatic (Page 14).
- For treatment of hypertension in astronauts without atrial fibrillation, the panel recommended avoidance of beta blockers and noted that ACEI are preferable for treatment of hypertension as they help prevent some of the cardiac fibrosis, scarring, remodeling and inflammation (Page 14).
- The risk of post-ablation recurrence is not amenable to mitigation by preventive care. Recurrences can be minimized by a more aggressive initial ablation procedure, and the impact of any such recurrence can be reduced by instituting close monitoring for early detection of recurrences (Page 16).
- The panel suggested that a limited invasive diagnostic study could be performed several months after the ablation to confirm that the pulmonary veins are indeed isolated and electrically silent and that no electrical reconnection has occurred, especially if a crewmember is being considered for a Mars mission. However, this is not the current established terrestrial clinical practice (Page 16).
- Although re-ablation would not be considered in the general population without a clinically significant recurrence, several of the panel members felt that it would be reasonable to re-ablate in the astronaut group of patients if there was evidence of an electrical reconnection, rather than to disqualify them from further space flight. However, the panel also cautioned that there is still insufficient evidence to support this practice, as case-controlled longitudinal studies have not been done to evaluate the risk versus the benefit of this proposed re-treatment (Pages 16-17).



- The panel was divided as to the length of time an astronaut with a history of ablated atrial fibrillation, history of hypertension and stroke, and a CHADS<sub>2</sub> score of 3 should remain on anticoagulation, with opinions ranging from one-year of treatment to indefinite treatment (Page 18).
- It was the panel's consensus and recommendation to not fly a crewmember who has had an atrial fibrillation-related stroke - either for short- or long-duration space missions (Page 18).

### **Atrial Fibrillation in Flight**

- The panel recommended supplying a rate control medication for Exploration-class missions in a quantity sufficient to treat at least one crewmember for the duration of the mission should atrial fibrillation manifest in flight (Page 19).
- For cases of paroxysmal atrial fibrillation occurring in flight, the panel's consensus was that the threshold for implementing rate control should be higher in microgravity than terrestrially and that a less aggressive rate control regimen should be used (Page 19).
- For cases of chronic persistent atrial fibrillation, the panel recommended that the ventricular response rate be kept below 100 (Page 19).
- The panel recommended that rate control be achieved using a mild AVN blockade with either a beta blocker or a calcium channel blocker, with the intention of blunting a maximal ventricular response to exercise to just below 200 BPM. Two-week ground testing was recommended for both beta blockers and calcium channel blockers, to evaluate for individual side effects and adverse reactions preflight (Page 19).
- The panel recommended using the Russian Braslets for treatment of in-flight atrial fibrillation-associated pulmonary edema, along with more conventional treatments such as diuretics while waiting for oral rate control medications to take effect, or while awaiting a deorbit opportunity (Page 21).
- The panel recommended treatment with aspirin at a daily dose of 325 mg for crewmembers who develop atrial fibrillation in flight, to lower the risk of thrombus formation in the atria and potential embolic stroke (Page 21).

### **Prevention of Atrial Fibrillation**

- The panel recommended minimizing risk factors for coronary artery disease, use of statins and ACEI, evaluating fish oil supplements (Omega-3 fatty acids), maintaining moderate aerobic fitness, and minimizing alcohol intake, all as possible atrial fibrillation preventive measures (Page 23).

### **Future Research**

- The panel suggested Holter data analysis, population-based studies, and genetic studies as potential future research projects that might help elucidate atrial fibrillation risk factors (Page 24).

## **VI. SUMMIT OUTCOME**

The Atrial Arrhythmia Summit brought together nationally and internationally recognized experts in cardiology, electrophysiology, exercise physiology, and space medicine in an effort to elucidate the mechanisms, risk factors, and management of atrial arrhythmias in the unique occupational cohort of the NASA astronaut corps. The summit generated valuable discussion and recommendations, which will be evaluated by NASA's Space Medicine Division over the next few weeks for incorporation into research, clinical, and operational practices.

The summit demonstrated the value of collaboration among NASA, the NASA supporting contractors, industry, and academia to promote astronaut health and support human endeavors in space.

## **VII. LIST OF ACRONYMS**

ACEI	Angiotensin Converting Enzyme Inhibitor
ADUM	Advanced Diagnostic Ultrasound in Microgravity Study
ASA	Acetylsalicylic Acid (aspirin)
AVN	Atrioventricular Node
AVNRT	Atrioventricular Node Reentrant Tachycardia
BPM	Beats Per Minute
CVA	Cerebrovascular Accident
CVP	Central Venous Pressure
EASI	Enterprise Advisory Services, Inc.
ECG	Electrocardiography
EP	Electrophysiology
EVA	Extravehicular Activity
ICV	Integrated Cardiovascular study
ISS	International Space Station
JSC	Johnson Space Center
MRI	Magnetic Resonance Imaging
NASA	National Aeronautics and Space Administration
PI	Principal Investigator
STS	Space Transportation System (Shuttle)
USAF	United States Air Force
UTMB	University of Texas Medical Branch
WPW	Wolf-Parkinson-White

## **VIII. APPENDIX 1: SUMMIT PANEL MEMBERS BIOGRAPHIES**

### **J.D. Polk, D.O., M.S., C.P.E., F.A.C.O.E.P. – Panel Chairman**

Dr. Polk is the Chief of Space Medicine at the NASA Johnson Space Center in Houston, Texas. He is responsible for the health care of the astronauts and the NASA workforce, mission medical support, occupational medicine, informatics, operational research, and medical and clinical operations. He is currently enrolled in the Masters in Medical Management program at the University of Southern California.

Dr. Polk attended medical school at the A.T. Still University in Missouri, and completed his residency in emergency medicine at Mt Sinai East and the Ohio University. He practiced emergency medicine for several years and then became the Chief Flight Surgeon of Metro Life Flight in Cleveland, Ohio. He served as the EMS Medical Director for the State of Ohio before coming to the National Aeronautics and Space Administration to lead medical operations. He is board certified in emergency medicine and medical management.

### **J. David Burkhardt, M.D., F.A.C.C.**

Dr. Burkhardt received his medical degree from the University of Louisville School of Medicine. He completed his residency in Internal Medicine at the University of Iowa in Iowa City. He then completed fellowships in Cardiovascular Medicine and Clinical Cardiac Electrophysiology from the University of Kentucky's Chandler Medical Center in Lexington and the Cleveland Clinic Foundation, respectively.

After completing his training, Dr. Burkhardt accepted a staff position in Cardiovascular Medicine as an Electrophysiologist at the Cleveland Clinic. In 2005, he was named Associate Program Director for the Clinical Cardiac Electrophysiology Fellowship training program and director of Clinical Electrophysiology curriculum at the Lerner Case Western Reserve School of Medicine at The Cleveland Clinic. Dr. Burkhardt currently serves on the staff of the Texas Cardiovascular Arrhythmia Institute at St. David's Medical Center in Austin Texas and, as of January 2008, also serves as the Chief Medical Officer at Stereotaxis, a company that introduces proprietary products and solutions built around the technology of magnetics for use in cardiac interventional medicine.

He has authored or co-authored more than 30 peer-reviewed publications, 10 book chapters, 100 abstracts, and has presented at numerous national and international meetings.

### **Mohamed H. Hamdan, M.D., M.B.A., F.A.C.C., F.H.R.S.**

Dr. Hamdan attended medical school at the American University of Beirut, Beirut, Lebanon, and completed an Internal Medicine residency at the University of Iowa Hospitals and Clinics. He then continued his medical training with a cardiology fellowship at Stanford University Hospital and an electrophysiology fellowship at the University of California - San Francisco.

Dr. Hamdan currently holds the positions of John and June B. Hartman Professor of Internal Medicine; Associate Chief, Division of Cardiology, and Director, Clinical Cardiac Electrophysiology, at the University of Utah. His prior faculty positions included Assistant Professor of Internal Medicine, University of Texas Southwestern Medical Center (1997); Associate Professor of Internal Medicine, University of Texas Southwestern Medical Center (2001); and Director, Clinical Cardiac Electrophysiology, University of Texas Southwestern Medical Center (2002). He has published extensively in the field of electrophysiology.

### **Rodney Horton, M.D., F.A.C.C.**

Dr. Horton earned his medical degree at the University of Texas Southwestern Medical School in Dallas, where he also completed his fellowship in electrophysiology. Also at UT Southwestern Medical School, he served as an Assistant Professor in Internal Medicine, Division of Cardiology. Dr. Horton currently serves on the staff of the Texas Cardiovascular Arrhythmia Institute at St. David's Medical Center in Austin Texas.

He is a recipient of the Southwestern Medical Foundation Scholarship for Academic Excellence and the Rotary International Fellowship for Study Abroad at the University of Heidelberg, Germany, in the field of medicine. Dr. Horton also presented as a guest lecturer at the prestigious Boston Atrial Fibrillation Symposium in 2006. At the top of the list of his most important accomplishments, though, Dr. Horton places all the patients he has helped during his career.

### **Benjamin D. Levine, M.D., F.A.C.C., F.A.C.S.M.**

Dr. Levine holds the positions of Distinguished Professor in Exercise Science, Professor of Medicine and Cardiology, at the University of Texas Southwestern Medical Center at Dallas, and is the Director of the Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas, where he also holds the S. Finley Ewing Jr. Chair for Wellness and the Harry S. Moss Heart Chair for Cardiovascular Research.

Dr. Levine graduated with an M.D. from Harvard Medical School, completed residency in Internal Medicine at the Stanford University Medical Center, Stanford, California, and then completed two fellowships: one in Environmental Physiology at the Shinshu University,

Matsumoto, Japan, and the other in Cardiovascular Disease at the University of Texas Southwestern Medical Center in Dallas. He has been the recipient of several prestigious awards, including The Henry Luce Foundation Scholarship (1985, national award to an individual showing outstanding promise for leadership in respective field), The Fulbright Scholarship (1989, international scientific exchange to August Krogh Institute in Copenhagen, Denmark), The Peter van Handel Memorial Award (1996, U.S. Olympic Committee award for contribution to sports science), The Michael J. Joyner Teaching Award from the Royal Danish Academy of Cardiovascular Sciences (2006, for outstanding teaching in cardiovascular physiology to international trainees), and a Citation Award from the American College of Sports Medicine (2007, for substantial and distinguished contribution to exercise science research). Trained in gravitational physiology by C. Gunnar Blomqvist, M.D., Dr. Levine has been either Principal or co-Investigator on virtually every dedicated life sciences mission focused on the cardiovascular system including SLS-1, SLS-2, D-2, and the Neurolab Mission. He is currently the Principal Investigator (PI) of the Integrated Cardiovascular Study, which is the largest cardiovascular experiment on the International Space Station and is actively examining arrhythmia risk associated with long-duration space flight. He has published extensively regarding cardiovascular adaptation to microgravity and is currently the Team Leader for the Cardiovascular Alterations Team of the National Space Biomedical Research Institute. In this capacity, he has organized and participated in numerous panels advising NASA flight surgeons regarding cardiovascular issues in space.

### **Andrea Natale, M.D., F.A.C.C., F.H.R.S.**

A native of Siracusa, Italy, Dr. Natale graduated summa cum laude from the University of Florence Medical School, Italy, and summa cum laude from the Catholic University School of Cardiology in Rome, Italy. He received his clinical training in cardiology at Methodist Hospital, Baylor College of Medicine in Houston, and at the University of Western Ontario in London, Ontario, Canada. After completing a clinical fellowship in cardiology and electrophysiology at the University of Western Ontario in 1991, he further trained in cardiology and electrophysiology at the University of Wisconsin, Sinai Samaritan Medical Center in Milwaukee.

Dr. Natale was head of the cardiovascular physiopathology section at the Italian Air Force's Aerospace Research Centre. He has served as director of the electrophysiology laboratory at Duke University and director of the electrophysiology program at the University of Kentucky, Lexington. He also headed the cardiac electrophysiology section of the cardiology department at the Cleveland Clinic Foundation in Cleveland, Ohio. Dr. Natale is currently Executive Medical Director of the Texas Cardiac Arrhythmia Institute at St. David's Medical Center in Austin, Texas.

Dr. Natale has served as a professor at a variety of prestigious universities, including Duke University and Stanford University. He has been an invited lecturer at more than 275

symposiums and conferences around the world, and is the author or co-author of hundreds of published articles on pacing and electrophysiology. In addition to serving on the editorial boards of numerous medical journals, he is editor in chief of the Journal of Atrial Fibrillation.

Dr. Natale believes the greatest thing he can give his patients is a normal life, free of medications. Dr. Natale pioneered a new circumferential ultrasound vein-ablation system to correct atrial fibrillation and performed the procedure on the world's first five patients. He also developed some of the current catheter-based cures for atrial fibrillation and was the first electrophysiologist in the nation to perform percutaneous epicardial radiofrequency ablation, which is a treatment for patients who fail conventional ablation. Dr. Natale feels it is crucial to continue to test new devices and concepts in order to move forward with the field of electrophysiology.

**Richard L. Page, M.D., F.A.C.C, F.A.H.A., F.H.R.S.**

Dr. Page received his undergraduate and medical degrees from Duke University, and served as a Sarnoff Fellow at Columbia Presbyterian in pharmacology during medical school. He trained in Medicine at the Massachusetts General Hospital. He then took his fellowships in Cardiology and Clinical Cardiac Electrophysiology at Duke.

Dr. Page served on the faculties at Duke and the University of Texas Southwestern before joining the University of Washington School of Medicine faculty in Seattle, Washington, in 2002 as Head of Cardiology and Robert A. Bruce Endowed Chair in Cardiovascular Research. In December, 2009 he moved to the University of Wisconsin School of Medicine & Public Health to become Professor and Chair of the Department of Medicine.

An expert in arrhythmias, including atrial fibrillation and sudden cardiac arrest, Dr. Page chairs committees for the American Heart Association and the American College of Cardiology Foundation and is President of the Heart Rhythm Society.





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